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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09 284,009	04 05 1999	CLAIRE E. LEWIS	550-128	1771

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EXAMINER

QIAN, CELINE X

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 03-11-2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/284,009

Applicant(s)

LEWIS ET AL

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 26 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 87-93, 95-101, 104, 109-116 and 120-125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 87-93, 95-101, 104, 109-116 and 120-125 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachments:

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement (PTO-115) (if any)
4) ☐ Interview Summary (PTO-413, Paper No. 1)
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

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DETAILED ACTION

Claims 87-93, 101, 104, 109-116 and 120-125 are pending in the application. Claims 94, 102, 103, 105-108, 117-119 and 126 are cancelled.

This Office Action is in response to the Amendment filed on 12/26/02.

Response to Amendment

The rejection of claims 90 and 101 under 35 U.S.C 112 second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 94 and 102-103 under 35 U.S.C 112 second paragraph is moot in light of Applicants' cancellation of the claims.

Claims 87-93, 101, 104, 109-116 and 120-125 stand rejected under 35 U.S.C. first paragraph for reasons set forth of the record and further discussed below.

Response to Arguments

In response to the rejection, Applicants argue that the specification as whole and exemplified by example 1, 2 and 5 has demonstrated that mononuclear phagocytes may be used to deliver drugs to hypoxic/ischemic sites where mononuclear phagocytes are typically present. Applicants argue that a claimed product needs only one enabled use to satisfy enablement and that an animal model demonstrating that a modified phagocyte home to a target site is sufficient to establish on enabled use. Applicants further argue that such a model is sufficient to extend homing capabilities of claimed cells to *in vivo* scenarios in other hosts irrespective of host response to vector or NOI. Applicants further cited *Cross v. Iizuka* to support the significance of

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evidence provided by Naylor Declaration is compelling evidence that one of ordinary skill in the art would have been able to use the claimed invention give the teaching of the specification and the generally advanced level of skill in the art.

The above arguments have been fully considered but deemed unpersuasive. The Examiner reiterates that the enablement rejection is based on how to use the mononuclear phagocytes and constructs based on the disclosure of the specification. The specification prophetically states that the constructs and phagocytes can be used in control of vascularization of developing tissues so as to promote vascularization, or directed to treating damages to the vascular system via an amputation, stroke, cardiac arrest, extreme hypertension, ischemia and burns. The specification further states that the expression of said construct in phagocytes in tumor hypoxic condition can be used to deliver prodrug or agents having cytotoxic effect to tumor cells *in vivo*. For such disclosed uses, the claimed invention is not enabled because the specification fails to teach a method of *in vivo* gene therapy that would overcome the technical difficulties discussed in the prior office action mailed on 11/28/01 (see page 6, 2nd and 3rd paragraph) and 8/26/02 (see page 5, 1st paragraph). Although the specification demonstrated that macrophages infiltrates to tumor sites in mice and expresses a marker gene such as GFP or β -gal, the specification fails to teach whether a therapeutic gene can be expressed at high and sustained level that is capable of achieve a therapeutic effect. Since the only disclosed uses are all directed to therapeutic uses or delivering a drug, the specification needs to support the enablement for such use wherein a therapeutic effect is achieved. In this case, the nude mouse model provided

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of successful treatment of hypoxic/ischemic disease for reasons set forth as record in the previous two office actions.

In response to Applicants' remarks regarding *in vitro* testing is significant (*Cross v. Iizuka*), the Examiner does not dispute this notion. However, in the instant case, the *in vitro* testing provided by the specification and the Naylor Declaration only demonstrate the expression of marker gene instead of a gene that can achieve a therapeutic effect. In view of the technical difficulties in the art of gene therapy, the specification fails to provide teachings to overcome such problems. Therefore, whether the mononuclear phagocyte can deliver a drug, or therapeutic gene to the hypoxic site and achieve a therapeutic effect in human is unpredictable. Thus, it would require undue experimentation to use the mononuclear phagocyte for its disclosed utility.

In response to Applicants' argument regarding safety and efficacy is not required by the enablement rejection (*Scott v. Finney*), the Examiner does not dispute this notion. However, the safety and efficacy issues discussed in the previous office actions represent part of the technical difficulties that contribute to the unpredictability for the successful gene therapy. Therefore, these issues are relevant in the context of achieving a therapeutic effect by the mononuclear phagocytes

Therefore, in view of the technical difficulties in gene therapy as discussed above and in the prior office action, one skilled in the art has to turn to the specification for guidance to practice the invention. However, the specification does not provide teachings and working examples on how to overcome these technical difficulties. As such, one skilled in the art would

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding

Marie Falk
MARIE FALK, Ph.D.
Supervisor

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Celine Qian, Ph.D.

March 5, 2003